PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0384-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000358	International filing date *(day/month/year)* 23.11.2004	Priority date *(day/month/year)* 24.11.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K51/04		
Applicant AMERSHAM HEALTH AS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.06.2005	24.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Dullaart, A Telephone No. +31 70 340-3290

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000358

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-26 as originally filed

   Claims, Numbers

   1-11 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10 in part

because:

☒ the said international application, or the said claims Nos. 10 in part relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000358

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	8
	No:	Claims	1-7,9-11
Industrial applicability (IA)	Yes:	Claims	1-9,11
	No:	Claims	10

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III.

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V.

1 Reference is made to the following documents:

D1 : WO 98/18496 A (NYCOMED IMAGING AS; COCKBAIN, JULIAN; KLAVENESS, JO; NAEVESTAD, ANNE;) 7 May 1998 (1998-05-07)

D2 : PONCHANT M ET AL: "Radiosynthesis of [tetrazoyl-^{11}C]irbesartan, a non-peptidic angiotensin II antagonist"
European Journal of Medicinal Chemistry, Editions Scientifique Elsevier, Paris, FR, vol. 32, no. 9, September 1997 (1997-09), pages 747-752, XP004094071 ISSN: 0223-5234

D3 : BURNS H D ET AL: "Development of [^{11}C]L-159,884: A Radiolabelled, Nonpeptide Angiotensin II Antagonist that is Useful for Angiotensin II, AT1 Receptor Imaging"
Applied Radiation and Isotopes, Pergamon Press Ltd., Exeter, GB, vol. 47, no. 2, February 1996 (1996-02), pages 211-218, XP004050601 ISSN: 0969-8043

D4 : WO 03/006070 A (AMERSHAM PLC; ARCHER, COLIN, MILL; WADSWORTH, HARRY, JOHN; ENGELL, TOR) 23 January 2003 (2003-01-23)

D5 : WO 03/051859 A (AMERSHAM PLC; BOUVET, DENIS, RAYMOND, CHRISTOPHE; WADSWORTH, HARRY, JO) 26 June 2003 (2003-06-26)

D6 : WO 03/006491 A (AMERSHAM HEALTH AS; CUTHBERTSON, ALAN; INDREVOLL, BAARD; SOLBAKKEN, MA) 23 January 2003 (2003-01-23)

2 Inventive Step

Document **D1** discloses (see passages cited in the international search report) radiolabelled Losartan.
Document **D2** discloses (see passages cited in the international search report) the

radiosynthesis of [tetrazoyl-^{11}C]irbesartan, a non-peptidic angiotensin II antagonist. Though the compound is labelled in the structure of irbesartan itself, it clearly is an agent having a moiety detectable in in vivo myocardial imaging, as is indicated in the passage on pages 749-750.
Document **D3** discloses (see passages cited in the international search report) the radiosynthesis of [^{11}C]L-159884, a non-peptidic angiotensin II antagonist. Though the compound is labelled in the structure of L-159884 itself, it clearly is an agent having a moiety detectable in *in vivo* imaging.

Neither of these compounds has "a linear or branched amino acid-comprising biomodifier or linker group". Therefore, this characteristic can be considered as distinguishing the present application from each of these prior art document.

In the present application, however, no comparison is made with prior art labelled Losartan compounds. In fact, since only the synthesis of certain compounds is given, their usefulness in (myocardial) imaging has yet to be established. The problem to be solved by the presently claimed compounds is therefore to provide alternative compounds for *in vivo* imaging of the angiotensin II receptors.

Documents **D4** to **D6** disclose (see passages cited in the international search report) the preferred chelator of the present application, linked to a different targeting group. This preferred chelator is also used for complexing ^{99m}Tc.

Starting from the usefulness of labelled Losartan in imaging the angiotensin II receptors, the skilled person would certainly use the label disclosed in any of **D4** to **D6** to label Losartan, thus arriving at the presently claimed invention without applying inventive skills. Therefore, the present application does not meet the requirements of Article 33.3 PCT for inventive step.

At this point, an exception can be made for the derivatives according to claim 8. In a letter of reply, the applicant has provided data showing an improved affinity of three Losartan derivatives for the AT1 receptor over the K_i of Losartan and of angiotensin II. According to the applicant, this increased affinity is based on the linker used. As the data concern Losartan conjugates only, it is not possible to extend this inventive step to conjugates of any other "organic groups having binding affinity for an angiotensin II receptor site".

Therefore, an inventive step cannot be acknowledged for present claims 1-7 and 9-11, but only for present claim 8.